ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction in Patients without Heart Failure

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ABSTRACT

BACKGROUND

The evidence supporting beta-blocker therapy after myocardial infarction was established before the introduction of modern coronary reperfusion therapy and secondary prevention strategies.

METHODS

In an open-label, randomized trial with blinded end-point evaluation, conducted in Denmark and Norway, we assigned patients who had had a myocardial infarction and who had a left ventricular ejection fraction of at least 40%, in a 1:1 ratio, to receive long-term beta-blocker therapy within 14 days after the event or no beta-blocker therapy. The primary end point was a composite of death from any cause or major adverse cardiovascular events (new myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias).

RESULTS

A total of 5574 patients underwent randomization and were included in the main analyses — 2783 in the beta-blocker group and 2791 in the no-beta-blocker group. After a median follow-up of 3.5 years (interquartile range, 2.2 to 4.6), a primary end-point event had occurred in 394 patients (14.2%) in the beta-blocker group and in 454 patients (16.3%) in the no-beta-blocker group (hazard ratio, 0.85; 95% confidence interval [CI], 0.75 to 0.98; P=0.03). Death from any cause occurred in 4.2% of the patients in the beta-blocker group and in 4.4% of those in the no-beta-blocker group; myocardial infarction occurred in 5.0% and 6.7%, respectively (hazard ratio, 0.73; 95% CI, 0.59 to 0.92), unplanned coronary revascularization in 3.9% and 3.9%, ischemic stroke in 1.6% and 1.3%, heart failure in 1.5% and 1.9%, and malignant ventricular arrhythmias in 0.5% and 0.6%. No apparent differences in safety outcomes were observed between the groups.

CONCLUSIONS

Among patients with a myocardial infarction and a left ventricular ejection fraction of at least 40%, beta-blocker therapy led to a lower risk of death or major adverse cardiovascular events than no beta-blocker therapy. (Funded by the Health South-East research program in Norway and others; BETAMI–DANBLOCK ClinicalTrials.gov numbers, NCT03646357 and NCT03778554.)

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*A list of the investigators in the BETAMI–DANBLOCK trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Munkhaugen and Kristensen and Drs. Prescott and Atar contributed equally to this article.

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Beta-blockers have been prescribed for secondary prevention after myocardial infarction on the basis of evidence from trials that were conducted more than 40 years ago.[1-5] Since then, the introduction of modern coronary reperfusion therapy and effective secondary preventive management has substantially improved long-term outcomes.[6] Furthermore, the relative distribution of causal risk factors such as smoking and high cholesterol levels in patients with myocardial infarction has changed, and high-sensitivity cardiac troponin measurements have improved diagnostic accuracy.[7,8] Although beta-blocker therapy is strongly recommended for patients with myocardial infarction and a reduced left ventricular ejection fraction (<40%),[9,10] its role is uncertain in patients with a preserved (≥50%) or mildly reduced (40 to 49%) left ventricular ejection fraction.[11,12] Trials evaluating beta-blocker use that have been conducted in the past 10 years are limited to those involving patients with a preserved left ventricular ejection fraction,[13] an ST-segment elevation myocardial infarction (STEMI),[14] or a chronic coronary syndrome.[15]

Beta-blockers have antiarrhythmic properties and reduce myocardial oxygen demand through negative inotropic and chronotropic effects.[16] Clinical trials from the era before coronary reperfusion therapies showed that beta-blockers reduced the risk of death from any cause and of new myocardial infarction after the index myocardial infarction.[1,2,4] In addition, beta-blocker therapy was associated with alleviation of angina symptoms and a lower incidence of ventricular arrhythmias and heart failure.[1,5,17] The BETAMI trial (Norwegian Beta-Blocker Treatment after Acute Myocardial Infarction in Revascularized Patients without Reduced Left Ventricular Ejection Fraction)[18] and the DANBLOCK trial (Danish Trial of Beta-Blocker Therapy after Myocardial Infarction without Heart Failure)[19] used similar protocols and were combined to evaluate whether long-term oral beta-blocker therapy would reduce the risk of death from any cause, new myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias (a composite end point) among patients hospitalized with myocardial infarction who have a preserved or mildly reduced left ventricular ejection fraction.[20]

Methods

Trial Design and Oversight

The combined BETAMI–DANBLOCK trial was a superiority trial with a PROBE (prospective, randomized, open-label, with blinded end-point evaluation) design.[20] The BETAMI and DANBLOCK trials were two trials, conducted at 25 sites in Denmark and 19 sites in Norway, respectively, that had almost identical designs and criteria for inclusion and exclusion. The protocols, available with the full text of this article at NEJM.org, were harmonized from the time of trial design in order to allow us to conduct joint analyses based on pooled data.[18-20] Because recruitment was lower than expected, owing partially to the coronavirus disease 2019 pandemic, the executive steering committees decided to combine the trials in May 2021 to ensure sufficient power to detect a possible effect of beta-blocker therapy on clinical outcomes.[20] Details on the rationale for combining the trials are provided in the Supplementary Appendix, available at NEJM.org. The trials were conducted in accordance with the ethical principles of the International Council for Harmonisation guidelines for Good Clinical Practice and received approval from the relevant authorities and ethics committees. The trials were overseen by independent data and safety monitoring boards, whose members monitored the overall conduct of the trials and performed analyses to assess patient safety at prespecified time points (more information is provided in the Supplementary Appendix).

Unrestricted grants from the Danish Heart Foundation, the Norwegian Health South-East research program, the Research Council of Norway, and the Novo Nordisk Foundation supported the trial. The executive steering committees designed the combined trial. The data were collected by the site investigators and analyzed by the trial statistician and the data manager, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first authors drafted the manuscript, which was then revised by the executive steering committees. All the authors reviewed the manuscript and approved it for publication.

Trial Population

Patients were eligible for participation if they provided written informed consent within 7 days (for

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inclusion in the BETAMI trial) or 14 days (for inclusion in the DANBLOCK trial) after having a type 1 myocardial infarction (BETAMI) or either a type 1 or type 2 myocardial infarction (DANBLOCK) and if they had a left ventricular ejection fraction of at least 40% (BETAMI) or more than 40% (DANBLOCK). The BETAMI trial included only patients who underwent coronary revascularization, whereas the DANBLOCK trial did not impose this criterion. Key exclusion criteria for both trials were a diagnosis of heart failure or other indications for beta-blocker therapy, as well as contraindications to beta-blocker therapy. The receipt of beta-blocker therapy before the myocardial infarction occurred was not an exclusion criterion. All the inclusion and exclusion criteria are shown in Figure S1 in the Supplementary Appendix.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, during the hospital stay, at an ambulatory visit, or remotely (by means of telephone or video calls) to receive beta-blocker therapy or to receive no beta-blocker therapy. Randomization was conducted with the use of online applications and was stratified according to trial center (in the BETAMI trial) and left ventricular ejection fraction (in the DANBLOCK trial). Because of the pragmatic design of the trial, which did not include physical follow-up visits and aimed to reflect contemporary practices, the choice and dose of the beta-blocker were left to the discretion of the treating physician. However, the maximum tolerated dose of metoprolol (long-acting version), bisoprolol, carvedilol, or nebivolol was recommended. For patients receiving a beta-blocker before enrollment who were randomly assigned to the no-beta-blocker group, the attending physicians were advised to discontinue the beta-blocker with a tapering plan and to consider alternative treatment, if necessary.

FOLLOW-UP

Follow-up was performed through linkage to the national Norwegian and Danish patient registries, with the use of the unique personal identification number given to all citizens at birth or at immigration. The registries have information on vital status and all hospital contacts, including diagnostic and procedural codes.[21,22]

Data on the beta-blocker dose and adherence to the assigned strategy (including checking that the patients in the no-beta-blocker group did not take beta-blockers) at 6 months after randomization were based on prescription fillings through linkage to the national Danish and Norwegian prescription registries (additional information is provided in the Supplementary Appendix). The registries are virtually complete owing to mandatory electronic reporting by all pharmacies and include data on the quantity and dose of all dispensed prescriptions.

CLINICAL AND SAFETY END POINTS

The primary end point was a composite of death from any cause or major adverse cardiovascular events (new myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias). Coronary revascularization included unplanned percutaneous coronary intervention or coronary-artery bypass grafting due to angina. Malignant ventricular arrhythmias were defined by the presence of ventricular arrhythmias or by resuscitated cardiac arrest of cardiac origin. The components of the primary end point were selected to capture the known pharmacologic mechanisms of beta-blockers and their clinically documented or plausible effects.[5,20]

The key secondary end points were each component of the primary end point and hospitalization for pacemaker implantation or second- or third-degree atrioventricular block. The safety end point requested by the Norwegian authorities was a composite of new myocardial infarction, heart failure, malignant ventricular arrhythmias, or death from any cause within 30 days after randomization.

All the events included in the primary, key secondary, and safety end points, except death from any cause, were adjudicated by two independent clinical end-point adjudication committees, whose members were unaware of the group assignments, after an initial screening for clearly defined nonevents (e.g., coronary revascularization planned at the time of the index event) by trial personnel who were also unaware of the group assignments. Details on the adjudication process and criteria are provided in the Supplementary Appendix.[23]

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STATISTICAL ANALYSIS

Using a power calculation for the combined trial, we estimated that approximately 950 primary end-point events would give the trial 80% power to detect a treatment effect with a hazard ratio of 0.83.[20] On the basis of blinded monitoring of event rates from the national registries during the trial, we anticipated that 5600 patients undergoing randomization would yield the desired 950 events after the last patient had been followed for a minimum of 12 months.

All analyses were prespecified and performed in the intention-to-treat population. The primary end-point analysis was conducted with a Cox proportional-hazards regression model with randomization group as the main covariate and with adjustment for the stratification variables of site and left ventricular ejection fraction. We had complete follow-up for all the patients except those who emigrated. The data for these patients were censored on the day of emigration or the last known date of contact with the trial. All remaining patients were followed until April 1, 2025. We estimated a hazard ratio for beta-blocker therapy as compared with no beta-blocker therapy, with a 95% confidence interval, and used a log-rank test to assess the null hypothesis of equality of the survival functions. The secondary end point of death from any cause was analyzed in the same manner. For secondary nonfatal events, the Fine–Gray competing-risk regression model was used, with death from any cause as the competing risk. A sensitivity analysis of the primary end point was performed in which follow-up time was limited (by means of right censoring) to 12 months. Prespecified analyses of the primary end point were performed in subgroups defined according to sex, age, country, type of myocardial infarction, left ventricular ejection fraction, beta-blocker dose, hypertension, and diabetes. The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Additional details are provided in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From October 2018 through January 2024, a total of 5622 patients underwent randomization. Of these, 5574 were included in the main analyses, because 22 patients did not meet inclusion criteria and 26 withdrew consent to follow-up (Fig. S2).

Information on the patients who underwent screening was available from all the DANBLOCK trial sites and from the three largest BETAMI sites. A total of 12,326 patients who met the inclusion criteria were assessed (Fig. S3); of these, 8694 patients (70.5%) were excluded, most commonly because of an indication for beta-blocker therapy (3717 patients [42.8%]). The median time from the index myocardial infarction to randomization was 2 days (interquartile range, 1 to 3). Baseline characteristics appeared to be well balanced between the groups (Table 1 and Table S1) and resembled the patient population with a myocardial infarction and left ventricular ejection fraction of at least 40% in European countries (see the Supplementary Appendix). Information on missing data is provided in Table S2.

The median age of the patients was 63 years (interquartile range, 55 to 71), and 20.8% were women. For 47.5% of the patients, a STEMI was the index event, 84.7% of the patients had a left ventricular ejection fraction of at least 50%, and 94.5% of the patients underwent a revascularization procedure. A total of 10.5% of the patients had a history of coronary artery disease, and 8.4% of the patients were receiving beta-blocker treatment before enrollment. At discharge, aspirin was prescribed in 95.0% of the patients, P2Y12-receptor blockers in 88.6%, and statins in 97.3%.

TREATMENT, ADHERENCE, AND FOLLOW-UP

Of the 2783 patients who were randomly assigned to receive beta-blocker therapy, long-acting versions of metoprolol were prescribed in 94.5%, with a median starting dose of 50 mg (interquartile range, 25 to 50); a dose of more than 50 mg was prescribed in 4.5% of the patients. The distributions of the beta-blocker classes and doses are shown in Tables S3 and S4.

At 6 months, 88.6% of the patients in the beta-blocker group and 88.7% of the patients in the no-beta-blocker group had remained adherent to the assigned strategy, and the median dose was unchanged (Tables S4 and S5). The median follow-up time was 3.5 years (interquartile range, 2.2 to 4.6). A total of six patients emigrated at a median of 1.59 years (interquartile range, 0.81 to 2.01) after randomization.

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Beta-Blockers (N=2783)	No Beta-Blockers (N=2791)
Median age (IQR) — yr	63 (55–71)	62 (55–71)
Female sex — no. (%)	601 (21.6)	561 (20.1)
Country — no. (%)		
Denmark	1352 (48.6)	1355 (48.5)
Norway	1431 (51.4)	1436 (51.5)
Risk factors		
Current smoker — no./total no. (%)	640/2279 (28.1)	614/2259 (27.2)
Median body-mass index (IQR)†	28 (25–30)	28 (25–31)
Hypertension — no./total no. (%)	1127/2783 (40.5)	1149/2791 (41.2)
Diabetes mellitus — no./total no. (%)	332/2783 (11.9)	363/2791 (13.0)
Hypercholesterolemia — no./total no. (%)	801/2775 (28.9)	808/2787 (29.0)
Median LDL cholesterol (IQR) — mmol/liter	3.3 (2.6–4.0)	3.3 (2.5–4.0)
Previous cardiovascular disease — no./total no. (%)		
Coronary artery disease	290/2783 (10.4)	298/2791 (10.7)
Peripheral artery disease	82/2777 (3.0)	83/2790 (3.0)
Stroke	81/2783 (2.9)	74/2791 (2.7)
Atrial fibrillation or flutter	52/2775 (1.9)	57/2789 (2.0)
Previous beta-blocker therapy — no./total no. (%)	248/2775 (8.9)	223/2788 (8.0)
Index MI — no./total no. (%)		
ST-segment elevation MI	1330/2782 (47.8)	1316/2791 (47.2)
Left ventricular ejection fraction of 40–49%	446/2779 (16.0)	406/2791 (14.5)
In-hospital treatment — no./total no. (%)		
Percutaneous coronary intervention	2582/2780 (92.9)	2577/2785 (92.5)
Coronary-artery bypass grafting	46/2780 (1.7)	56/2785 (2.0)
No revascularization	176/2783 (6.3)	170/2791 (6.1)
Medication at discharge ≤30 days after MI — no./total no. (%)		
Aspirin	2637/2783 (94.8)	2656/2791 (95.2)
P2Y12-receptor blocker	2478/2783 (89.0)	2463/2791 (88.2)
Anticoagulants	121/2776 (4.4)	99/2787 (3.6)
ACE inhibitor or ARB	1143/2776 (41.2)	1266/2787 (45.4)
Statin	2692/2776 (97.0)	2719/2787 (97.6)
Ezetimibe	363/2776 (13.1)	339/2787 (12.2)

* Data on race and ethnic group were not collected. To convert LDL cholesterol levels from millimoles per liter to milligrams per deciliter, multiply by 38.67. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, IQR interquartile range, LDL low-density lipoprotein, and MI myocardial infarction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

END POINTS

A primary end-point event occurred in 394 of 2783 patients (14.2%) assigned to the beta-blocker group and in 454 of 2791 patients (16.3%) assigned to the no-beta-blocker group (hazard ratio, 0.85; 95% confidence interval [CI], 0.75 to 0.98; P=0.03) (Fig. 1 and Table 2). A total of 23% of the events evaluated by the clinical end-point adjudication committee were rejected (Table S6). The reasons for rejection of myocardial infarc-

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Table 2. Primary, Secondary, and Safety End Points.*

End Point	Beta-Blockers (N=2783)	No Beta-Blockers (N=2791)	Hazard Ratio (95% CI)
		number (percent)	
Primary end point†			
Composite of death from any cause, myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias‡	394 (14.2)	454 (16.3)	0.85 (0.75–0.98)
Secondary end points			
Death from any cause	118 (4.2)	124 (4.4)	0.94 (0.73–1.21)
Myocardial infarction	138 (5.0)	186 (6.7)	0.73 (0.59–0.92)
Unplanned coronary revascularization	108 (3.9)	110 (3.9)	0.99 (0.76–1.29)
Ischemic stroke	45 (1.6)	35 (1.3)	1.30 (0.84–2.03)
Heart failure	42 (1.5)	52 (1.9)	0.78 (0.52–1.18)
Malignant ventricular arrhythmias‡	15 (0.5)	18 (0.6)	0.82 (0.42–1.64)
Implantation of a pacemaker or second- or third-degree atrioventricular block	49 (1.8)	49 (1.8)	1.00 (0.67–1.49)
Safety end point			
Composite of death from any cause, myocardial infarction, heart failure, or malignant ventricular arrhythmia at 30 days	21 (0.8)	32 (1.1)	

* For all end points except the primary composite end point and the secondary end point of death from any cause, death before an event occurred was counted as a competing risk, and cause-specific hazards are shown. The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis tests.
† P=0.03 for the comparison of beta-blocker therapy with no beta-blocker therapy.
‡ Malignant ventricular arrhythmias include ventricular arrhythmia and resuscitated cardiac arrest of cardiac origin.

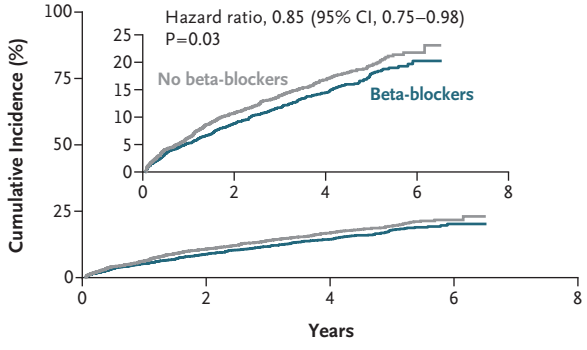

Figure 1. Time-to-Event Analysis of the Primary End Point.
The primary end point was a composite of death from any cause, myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias. The inset shows the same data on an expanded y axis.

tion events are listed in Table S7. Death from any cause occurred in 4.2% of the patients in the beta-blocker group and in 4.4% of the patients in the no-beta-blocker group (hazard ratio, 0.94; 95% CI, 0.73 to 1.21). A new myocardial infarction occurred in 5.0% of the patients in the beta-blocker group and in 6.7% of the patients in the no-beta-blocker group (hazard ratio, 0.73; 95% CI, 0.59 to 0.92). Additional details on the new myocardial infarctions are shown in Table S8. Unplanned coronary revascularization occurred in 3.9% of the patients in each of the groups (hazard ratio, 0.99; 95% CI, 0.76 to 1.29), and ischemic stroke occurred in 1.6% of the patients in the beta-blocker group and in 1.3% of the patients in the no-beta-blocker group (hazard ratio, 1.30; 95% CI, 0.84 to 2.03). Heart failure occurred in 1.5% of the patients in the beta-blocker group and in 1.9% of the patients in the no-beta-blocker group (hazard ratio, 0.78; 95% CI, 0.52 to 1.18), and malignant ventricular arrhythmias occurred

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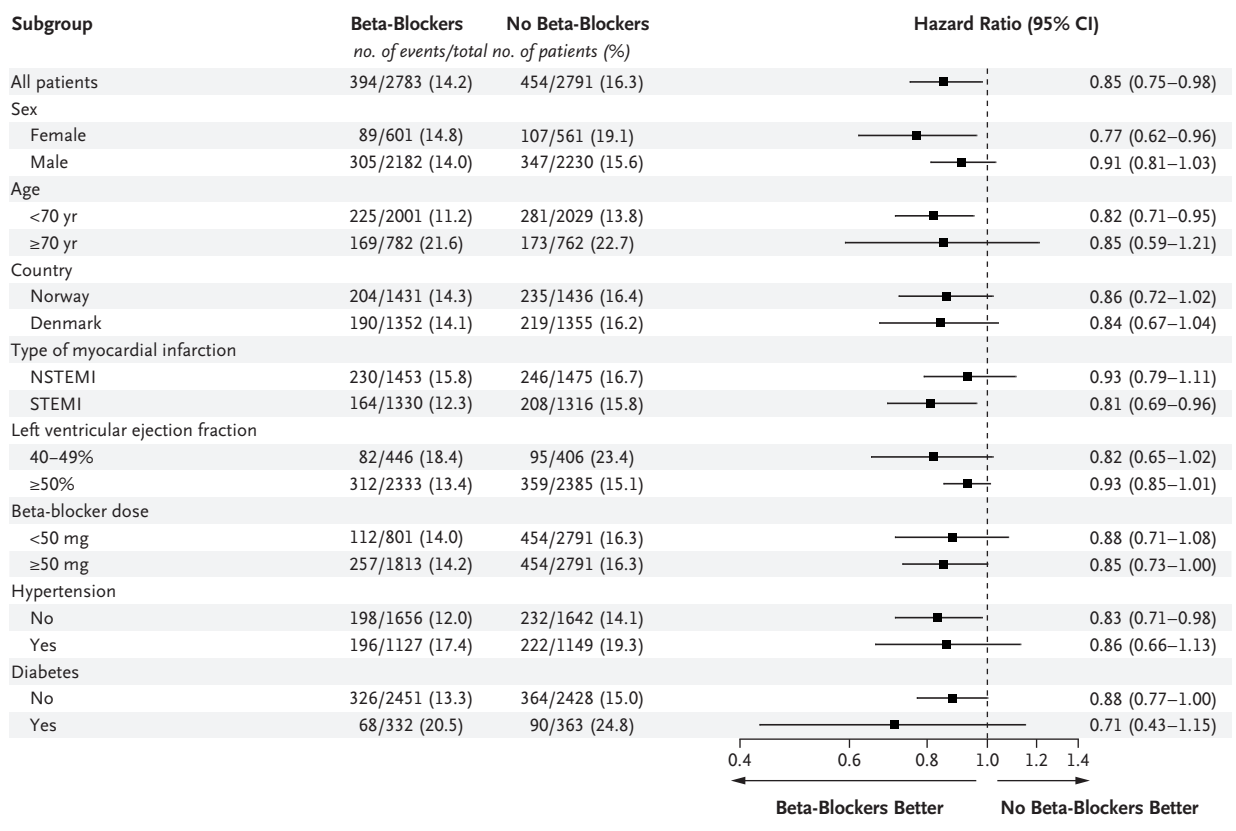

Figure 2. Primary End-Point Events in Prespecified Subgroups.

For left ventricular ejection fraction, data were missing for 4 patients in the beta-blocker group; for beta-blocker dose, data were missing for 169 patients in the beta-blocker group. The beta-blocker included here was metoprolol. Data on the beta-blocker dosage were not collected for the participants in the no-beta-blocker group, so each beta-blocker dose subgroup is compared with all the participants in the no-beta-blocker group. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

in 0.5% and 0.6%, respectively (hazard ratio, 0.82; 95% CI, 0.42 to 1.64) (Table 2 and Figs. S4 to S18). The incidence of hospitalization for pacemaker implantation or second- or third-degree atrioventricular block appeared to be similar in the two groups (Table 2 and Fig. S10).

In a prespecified analysis restricted to 12 months of follow-up, a primary end-point event occurred in 147 patients (5.3%) in the beta-blocker group and in 181 patients (6.5%) in the no-beta-blocker group (hazard ratio, 0.80; 95% CI, 0.64 to 0.99) (Figs. S11 and S19). The results for the primary end point appeared to be consistent across the prespecified subgroups (Fig. 2).

SAFETY

A safety end-point event (death from any cause, myocardial infarction, heart failure, or malignant ventricular arrhythmia at 30 days) occurred in 21 patients (0.8%) in the beta-blocker group, as compared with 32 patients (1.1%) in the no-beta-blocker group (Table 2). The incidence of serious adverse events appeared to be similar in the two groups (Table S9).

DISCUSSION

In this randomized, open-label trial with blinded end-point evaluation, conducted in Denmark and Norway, long-term beta-blocker therapy reduced the incidence of death from any cause or major adverse cardiovascular events (the composite end point) in patients with a myocardial infarction and a preserved or mildly reduced left ventricular ejection fraction. Beta-blocker therapy may have decreased the cumulative incidence of new

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myocardial infarction, but there was no apparent difference between patients who received beta-blockers and those who did not in the risk of death from any cause, heart failure, malignant ventricular arrhythmias, unplanned coronary revascularization, or ischemic stroke. The results appeared to be similar in the two participating countries and to be consistent across the prespecified subgroups.

Randomized, placebo-controlled trials that were conducted in the era before coronary-artery revascularization showed that short- and long-term beta-blocker therapy reduced the risk of death from any cause and reinfarction among patients with myocardial infarction.[1-5] Exploratory analyses also revealed effects on heart-failure hospitalizations and ventricular arrhythmias. These trials did not exclude patients with heart failure, and left ventricular ejection fraction was not reported, which suggests that some survival benefit of beta-blockers might have been derived from subgroups with heart failure.[24] In the BETAMI–DANBLOCK trial, we excluded patients with clinical evidence of systolic heart failure or with a left ventricular ejection fraction of less than 40%. Furthermore, almost all the patients in our trial underwent coronary revascularization and received dual antiplatelet therapy and a statin at hospital discharge, interventions that are known to improve survival after a myocardial infarction.

Despite relatively modest beta-blocker doses and a crossover of 11.4% in the beta-blocker group and of 11.3% in the no-beta-blocker group at 6 months, factors that could bias the results toward equipoise, beta-blocker therapy resulted in a lower incidence of a primary end-point event than no beta-blocker therapy after a median follow-up of 3.5 years. An indication of a beneficial effect of beta-blocker therapy already appeared to be present at 12 months of follow-up. Although the trial was not designed to evaluate any secondary end points statistically, there appeared to be a lower incidence of new myocardial infarctions among patients assigned to the beta-blocker group. The majority of these events were non-STEMIs (80%), 65% occurred in patients who had undergone coronary revascularization, and only 11% of the patients had a left ventricular ejection fraction of less than 40% (Table S8).

In trials from the era before routine reperfusion, myocardial infarction was the primary nonfatal outcome that was reduced by beta-blockers.[2,4,5] A more recent trial involving 45,852 patients, most of whom had STEMI, showed that early and short-term treatment with metoprolol led to a significantly lower risk of myocardial infarction than placebo (2.0% vs. 2.5%; P=0.001), but not to a lower risk of death from any cause (7.7% vs. 7.8%).[25] Beta-blockers reduce myocardial oxygen demand by exerting negative chronotropic and inotropic effects.[16] In addition, beta-blockers are believed to enhance diastolic perfusion time, improve myocardial metabolism, and positively influence coronary microvascular and platelet function, thereby contributing to their overall efficacy in preventing myocardial infarction.[16,26] Our findings suggest that despite advances in contemporary myocardial infarction treatment, these beneficial effects of beta-blocker therapy remain clinically relevant.

Three open-label trials within the past decade have addressed beta-blocker therapy after myocardial infarction. In CAPITAL-RCT (Carvedilol Post-Intervention Long-Term Administration in Large-Scale Randomized Controlled Trial), 801 patients with STEMI and a left ventricular ejection fraction of more than 40% were randomly assigned to receive carvedilol or not to receive beta-blocker therapy.[14] During a median follow-up of 3.9 years, 6.8% of the patients in the carvedilol group and 7.9% of the patients in the no-beta-blocker group had a primary end-point event — a composite of death, myocardial infarction, hospitalization for heart failure, or hospitalization for acute coronary syndromes (hazard ratio, 0.75; 95% CI, 0.47 to 1.16; P=0.20).[14] The open-label REDUCE-AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction) trial included only patients with a preserved left ventricular ejection fraction but, like our trial, used registry-based end points; however, these events were not independently adjudicated. The REDUCE-AMI trial showed no effect of beta-blocker therapy on the risk of death from any cause or new myocardial infarction (the primary composite end point) (hazard ratio, 0.96; 95% CI, 0.79 to 1.16).[13] This result appears to be consistent with the results of our analyses in subgroups of patients with preserved left ventricular ejection fraction (hazard ratio, 0.93; 95% CI, 0.85 to 1.01). Finally, the ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hos-

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pitalization) noninferiority trial included patients in stable condition with coronary artery disease who were receiving a beta-blocker at a median 2.9 years after myocardial infarction. The results of this trial showed that interruption of beta-blocker therapy was not noninferior to continuation of beta-blocker therapy with respect to a composite end point of death, myocardial infarction, stroke, or hospital admission for cardiovascular reasons.[15] However, comparing the ABYSS trial with other contemporary trials that enrolled patients at the time of their myocardial infarction, including the REBOOT (Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction) trial,[27] is challenging because these trials do not address the same clinical question.[13-15]

Patients with a mildly reduced left ventricular ejection fraction were included in our trial specifically because the existing evidence supporting beta-blocker therapy in this subgroup is limited, despite a plausible therapeutic benefit. Early randomized trials that found a beneficial effect of beta-blockers primarily included patients with Q-wave myocardial infarctions and more extensive myocardial damage, which are typically associated with a reduced left ventricular ejection fraction.[1,2,4] Recently, findings from CAPITAL-RCT showed that carvedilol reduced the risk of cardiac death, myocardial infarction, or heart failure (a secondary composite outcome) among patients with a mildly reduced left ventricular ejection fraction, but not among those with preserved left ventricular ejection fraction.[28] Although our trial was not powered for analysis of the results in the subgroup of 852 patients with a mildly reduced left ventricular ejection fraction, the hazard ratio for the primary end point was 0.82 (95% CI, 0.65 to 1.02). These findings underscore the need for future pooled analyses of contemporary trials, which may help identify the patient populations that may benefit from beta-blocker therapy after myocardial infarction.

Our trial has limitations that must be acknowledged. First, the trial was performed as an open-label trial. To mitigate this limitation, all components of the primary end point were identified through registries, and the events were adjudicated by a committee whose members were unaware of the group assignments. Second, the DANBLOCK and BETAMI trials were combined, and the primary end point was harmonized while the trials were ongoing. Completion of each trial individually was not feasible because of low enrollment and a low incidence of events, factors that would have given the individual trials insufficient power to detect a clinically meaningful treatment effect. The original trials shared similar inclusion and exclusion criteria and were designed and conducted in close collaboration. The decision to combine the trials was made in May 2021, nearly 4 years before the end of the follow-up period and without knowledge of the results for the end points. Finally, nearly all the patients in the BETAMI–DANBLOCK trial received treatment with long-acting versions of metoprolol at a median starting dose of 50 mg, and therefore the findings may not be generalizable to other beta-blocker classes and higher doses.

In this randomized, controlled trial, oral beta-blocker therapy led to a lower risk of death from any cause or major adverse cardiovascular events (the composite primary end point) than no beta-blocker therapy among patients with a myocardial infarction and a preserved or mildly reduced left ventricular ejection fraction.

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